Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attachment is captioned "Appendix. Version with Markings to Show Changes Made."

Information Disclosure Acknowledgement

Applicants are thankful to the Examiner for entering and considering the Supplemental Information Disclosure Statement with form PTO 1449 submitted on May 23, 2000.

Patentability Under 35 USC § 112

Claim 111 is rejected under 35 U.S. C. 112, second paragraph as allegedly indefinite, for reasons of record. Applicants have amended the subject claim in conformity with the previous amendments to claims 39, 131, and 139, thereby obviating the rejection.

Claims 15, 16, 30, 31, 36, 37, 39, 65- 69, 71, 72, 78, 81, 82, 105, 106, 109-111, 113, 114,117, 127, 128, 130, 131, 133, 135, 138, 139 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which is allegedly not enabled by the disclosure. This rejection is directed to a deposit requirement, and the Examiner has called for Applicants to submit evidence that the necessary deposit of JS cp45 has been made under Budapest conditions, and to amend the specification to refer to the deposit. Applicants forwarded an official Certification of the deposit on December 7, 2000 showing that the requested deposit was made. Applicants provide herewith an appropriate Declaration of Dr. Brian R. Murphy relating to the deposited material. Concerning the date of the deposit, the specification already discloses that the deposit was made on August 21, 1997 (see p. 79, lines 4-9). On this basis, withdrawal of the rejection is earnestly solicited.

Patentability Under 35 USC §§ 102 and §103

Claims 1-4, 6, 7, 10-17, 20, 21, 26, 27, 30, 33-40, 43, 44, 47-49, 52, 54, 56, 57, 59, 6185, 88-91, 93, 94, 96-116, 118, 120-143 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by or, in the alternative, under 35 U.S. C. 103 (a) as allegedly obvious over, Belshe et al. (5,869,036), for reasons of record.

Procedural Considerations and Status of Evidence in Record

The Examiner states that Applicant's prior submissions filed 6/19/2000 and 4/9/2001 have been fully considered but were not found persuasive. The Examiner initially dismisses these submissions with a blanket characterization that they are considered to be "argument of counsel, including many assertions regarding facts, not actual evidence." The Examiner further states that Applicants' prior submissions "were not ignored, though their probative weight is not the weight of actual evidentiary showings."

Further confusing the issue of what factual components of Applicants' previous submissions were actually considered by the Office as factual or evidentiary in nature, the Examiner states that:

> For the sake of argument . . . the Office assumed all of the asserted "facts" could be documented by material in the specification or in printed publications or by declaration. Even based on this assumption, the Office remains unpersuaded and thus, did not require the same information presented in another format.

Applicants respectfully request clarification of these comments. It is clearly not appropriate to characterize Applicants' submissions of 6/19/2000 and 4/9/2001 as purely "argument of counsel". The facts presented in these submissions were developed through detailed technical discussions between Applicants and their attorney--all of whom have extensive technical experience in the relevant arts. However, it is clear from the record that this evidence was not responded to in substantive detail in the current record to assist Applicants in resolving outstanding issues to advance prosecution of the application.

In reference to these procedural concerns, Applicants note that MPEP section 707.07 provides the following directions for complete examination of patent applications:

> The examiner must address all arguments which have not already been responded to in the statement of the rejection.
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> The examiner must, however, address any arguments presented by the application which are still relevant to any references being applied.

The instant record cannot be considered properly developed if, on one hand, the Examiner characterizes Applicants' assertions of fact to fall short of "actual evidentiary showings", while on the other hand states that "the Office assumed all of the asserted 'facts' could be documented" and therefore need not be presented "in another format."

To resolve this ambiguity, Applicants have filed herewith a detailed Declaration of Dr. Brian Murphy, an inventor in the application, that sets forth previously submitted evidence and provides additional evidence and opinion based thereon, responsive to the issues raised by the Office in the present and former Office Actions. Applicants respectfully request that the Examiner enter this material in the record and consider it fully and responsively in any subsequent Official Action.

Applicants' Burden of Proof in Rebutting the Alleged Anticipatory Reference

Considering the burden of proof that the Office has placed on Applicants, this aspect of the record is also contrary to established authority. Throughout the Office Action, the Examiner contends that Applicants must prove by "clear and convincing evidence" that the disclosure of Belshe et al., is nonenabling for the subject matter presently claimed (Office Action Paper No. 22 at pp. 5 and 7). The Examiner also attaches this strict "presumption of validity" to subject matter in the Belshe et al. specification. For example, at page 5 of the Office Action the Examiner cites a passage

at column 9, line 55 to column 10, line 40 that allegedly discusses "producing a cDNA and producing a virus."

Contrary to the Office's position, this prophetic statement by Belshe et al. is not entitled to any presumption of validity. Moreover, even if such a presumption properly attaches to the hypothetical teachings of Belshe's patent specification, the burden placed on Applicants is not so stringent as the burden applied by the Examiner in the instant case.

The so-called "presumption of operability" relied upon by the Office (35 U.S.C. § 282) relates only to subject matter that is claimed in an issued U.S. Patent. Specifically, Section 282 of the Act reads:

> Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims. . . . (emphasis supplied).

Outside of this limited presumption, statements in a patent specification are not accorded any specific presumption of validity. On this basis, the alleged teachings of Belshe et al. regarding enablement of a recombinant Parainfluenza virus from cDNA are not entitled to the blanket presumption of validity conferred by the Office in reliance upon 35 U.S.C. § 282.

Even if the purported teachings of Belshe et al. relied upon by the Office were in fact entitled to a presumption of validity under 35 U.S.C. § 282, as alleged, the Office must still consider all of the evidence presented by Applicants--in full, responsive, substantive detail. Moreover, Applicants' evidence, and the scientific conclusions based thereon, must be viewed by the Office as presumptively correct--unless the Office provides substantiated evidence that is "inconsistent" with Applicants' evidence and conclusions. See, e.g., In re Marzocchi et al., 169 USPQ 367 (CCPA 1971).

Regardless of the status of prophetic statements in the Belshe et al. disclosure, it is clear that Applicants burden is not to rebut any presumptively valid teachings by "clear and convincing evidence", as maintained by the Office. On the contrary, controlling authority specifically provides that Applicants need merely show by

"a preponderance of the evidence" that any presumptively valid subject matter is inoperable (see, e.g., MPEP § 716.07, citing In re: Sasse, 207 USPQ 107 (CCPA 1980). From Applicants standpoint, this means that subject matter specifically and distinctly claimed in the Belshe et al. patent (not all subject matter prophesied in the Belshe et al. specification as a whole) may be entitled to a presumption of validity--but this presumption is overcome by a preponderance of evidence showing that the claimed subject matter is inoperable in view of the limited teachings of the Belshe et al. disclosure. This is precisely the analysis presented by the Federal Circuit's predecessor court in In re: Sasse, supra. Accordingly, Applicants respectfully request clarification and reconciliation of this burden of proof as compared to the "clear and convincing evidence" standard repeatedly applied by the Office in the instant case, in a manner that rectifies any prejudice to Applicants.

Analysis of the Belshe et al. Teachings

As noted previously, the standard for anticipation by patenting requires a full enabling disclosure, as is true for printed publications, i.e., the cited patent must disclose the invention in such full, clear and exact terms as to enable any person skilled in the art to which the invention relates to practice it. As explained by the Federal Circuit in In re Donohue, 226 USPQ 619, (Fed. Cir. 1985).

> It is well settled that prior art under 35 U.S.C. § 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it.
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> ***
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> [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. (emphasis supplied, citing In re Borst, 45 USPQ 544, 557 (CCPA 1965), *cert. den.* 382 U.S. 973, 148, USPQ 771 (1966).

It is clear from the instant record that Belshe et al. fail to provide any working examples of the subject matter set forth in Applicants' pending claims. The Office dismisses this requirement altogether, even while asserting that the art surrounding the invention is highly unpredictable, and even though Applicants' disclosure is rejected for nonenablement (see below) despite the provision of extensive working examples therein. This dismissal is respectfully submitted to be contrary to the evidence of record,

and at odds with controlling authority. In the latter context, it is understood that working examples are not *per se* necessary to meet the enablement requirements of 35 U.S.C. § 112. However, the Forman and Wands decisions previously discussed in the record make it clear that failure to provide working examples demonstrating operability of an invention is an important factor to consider in determining enablement. This principle is embraced by the Patent Office and further emphasized in the context of unpredictable inventions in MPEP § 2164.02, as follows:

> Lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art (emphasis supplied).

In the instant case, the Office concededly bases its principal rejection of Applicants' claims on the literal, prophetic content of the Belshe et al. patent. To maintain this ground of rejection, the record must clearly establish that the Belshe et al. disclosure fulfills all of the enablement requirements of 35 U.S.C. § 112 applicable to the instant claims. The evidence of record, however, including the evidence presented in the accompanying Declaration of Dr. Brian R. Murphy, M.D. (incorporated herein by reference) clearly evinces that the Belshe et al. disclosure fails to meet this standard. Likewise, the evidence presented herein and previously made of record clearly establishes that the Belshe et al. reference fails to disclose or suggest the subject matter of the pending claims within the meaning of 35 U.S.C. § 103.

Referring to the Declaration of Dr. Murphy, Applicants respectfully submit that their basic cDNA recovery method for producing recombinant PIVs, and particularly for generating recombinant PIVs for development as vaccine candidates, is neither taught nor suggested by the Belshe et al. reference (viewed in any combination with general knowledge in the art and/or secondary references of record). Dr. Murphy's Declaration sets forth detailed facts supportive of the conclusion rendered at ¶ 7 that:

> [T]he Belshe et al. patent (alternatively, the '036 patent) does not provide sufficient description and guidance to permit a person of ordinary skill in the art (at either the time the Belshe et al. patent or the current application was filed) to recover a recombinant parainfluenza virus (PIV) from cDNA. On the contrary, the Belshe et al. specification only hypothetically discusses the possibility

> of recovering a recombinant PIV from cDNA. No such cDNA nor recombinant PIV is actually described in structural terms that would qualify as a "written description" of such materials, and it is apparent that no "working example" of a cDNA encoding a recombinant PIV, nor of an actual recombinant PIV, is provided by the Belshe et al. disclosure. Additionally, considering the level of predictability in the art prior to the discoveries presented in the instant application, the teachings of Belshe et al. would not have been considered to provide an "enabling" disclosure of the presently claimed invention. That is to say, Belshe et al. offer such limited direction and guidance that, even when supplemented by available knowledge in the art at the time the instant application was filed, the skilled artisan would not have considered the public to be placed "in possession of" a recombinant PIV produced from cDNA. This conclusion, and the related conclusions below, relate to the fundamental technology of the present invention, i.e., successful recovery of a viable, self-replicating, recombinant PIV from cDNA. It is even more clear that certain detailed aspects of the invention, e.g., involving identification and manipulation of attenuating mutations and their introduction, singly and in combination, into a recombinant PIV, and successful recovery of chimeric PIVs, and attenuated chimeric PIVs, are neither disclosed nor suggested by Belshe et al.

Additional facts and conclusions are presented in Dr. Murphy's Declaration to support the conclusion that Belshe et al. fail to render the presently claimed invention "obvious" within the meaning of 35 U.S.C. § 103. As stated by Dr. Murphy in paragraph 8 of his Declaration, "the limited teachings of Belshe et al. fail to provide a practical suggestion or motivation that would have led the skilled artisan to undertake production of a recombinant PIV from cDNA with a 'reasonable expectation of success'".

> Considering the poorly developed state of knowledge and high degree of unpredictability in the art, among other technical challenges discussed below, to achieve this goal without the benefit of the instant disclosure would have been viewed by the skilled artisan as requiring such extensive and uncertain experimentation that would have been characterized as "undue" experimentation--unattended by a "reasonable expectation of success". The same facts, set forth below, that support this conclusion also point to a

> conclusion that the instant disclosure provides "unexpected results" in the successful production of a recombinant PIV from cDNA. Concerning more detailed aspects of the invention, the results provided by the instant disclosure allow production of singly and multiply attenuated, recombinant PIVs, chimeric PIVs, and attenuated chimeric PIVs, that are sufficiently infectious in a mammalian host to generate a desired immune response yet are suitably attenuated for selection and development as PIV vaccine candidates. That these novel results were achieved within the instant invention was even more surprising that the basic recovery of recombinant PIV, based on the limited teachings of Belshe et al. combined with general knowledge in the art at the time of the invention.

Considering now the facts of record that support Dr. Murphy's conclusions, Applicants note that the Belshe et al. specification fails to provide a single example of a recombinant PIV recovered from a cDNA. As noted previously and evidently undisputed by the Office, the Belshe et al. reference is limited in its teachings to a simple *in vitro* complementation assay described to evaluate temperature sensitivity. Dr. Murphy points out in his Declaration, this limited study is attended by fundamental flaws in its design and interpretation. Nonetheless, Even if the complementation assay results reported Belshe et al. were accepted at face value, there is no reasonable scientific basis for extrapolating these findings into the context of a complete, infectious virus. More important and apparent, these reported results cannot reasonably be extended to forecast a "reasonable expectation of success" for producing a recombinant PIV that is viable, attenuated, and immunogenic *in vivo* (Murphy Declaration at ¶¶ 10 and 12-13).

In contrast to the deficient teachings of Belshe et al., the instant application provides detailed working examples that detail production and employment of cDNAs to yield successful recovery of (1) recombinant wild type human parainfluenza virus type 3 (PIV3); (2) multiple recombinant PIV3s containing well defined single attenuating mutations; (3) multiple recombinant PIV3s containing more than one attenuating mutation in combination; (4) a chimeric PIV3-1 virus in which the HN and F open reading frames (ORFs) of wild type PIV3 were replaced with ORFs encoding the counterpart HN and F proteins of PIV1; and (5) viable, immunogenic derivatives of

chimeric PIV3-1 having defined attenuating mutations incorporated in the chimeric virus (Murphy Declaration at ¶ 11).

Briefly considering the above-noted deficiencies of Belshe et al. as noted by Dr. Murphy, it is readily apparent that the complementation assay described by Belshe et al. was a rudimentary system in which a plasmid expressing a wild type L protein in a transfected cell monolayer reportedly increased the level of replication of PIV3 cp45. The system notably failed to include a control plasmid containing the cp45 mutations, whereby the differences identified in the complementation assay cannot be ascribed to sequence differences between the wild type and cp45 PIV3 L protein, contrary to the assertions of Belshe and coworkers (Murphy Declaration at ¶ 11). In addition, the L cDNA employed by Belshe et al. was never evaluated for its effect on replication of wild type HPIV3. This is considered by Dr. Murphy to represent "a critical control" that would preclude the possibility that the observed increase in virus replication was simply due to increased expression of L protein (an aberration defined as a "dose effect" rather than true complementation of a *ts* defect) (Id.) The assay of Belshe et al. (see Table 3) is also considered by Dr. Murphy to be unreliable in other crucial aspects. For example, reported positive results in the complementation complementation assay contain internal inconsistencies and lack essential verification of important experimental controls. These inconsistencies would have been apparent to the skilled artisan and "would have detracted significantly from the motivation provided by the cited reference and the expectation of success that the artisan would have to practice the presently claimed invention as allegedly taught or suggested by Belshe et al." (Murphy Declaration at ¶ 12).

Yet additional evidence is provided in paragraph 13 of Dr. Murphy's Declaration that only as few as 3 or 4 cells, and certainly no more than 330 cells, in the complementation assay of Belshe et al. successfully produced virus, "whereas the remaining several million failed to produce a single particle." On this basis, Dr. Murphy concludes that:

> [E]ven if the complementation is accepted as authentic, it is of such a low efficiency that its significance is highly doubtful. In any case, there are no means for extrapolating findings from such a complementation assay to infectious

> virus. Thus, the 20-fold increase in the replication seen in the complementation assay cannot be extrapolated to predict or understand the magnitude of the contribution of the L protein mutations to the ts phenotype of cp45, nor what the biological properties of a hybrid virus carrying only these mutations might be. At best, the findings are simply suggestive that the L gene mutations might contribute to some undefined portion of the temperature sensitivity of the cp45 virus.

Also in paragraph 13 of his Declaration, Dr. Murphy notes that the complementation assay of Belshe "relates only to the *ts* phenotype of cp45, and does not address the attenuation phenotype *in vitro* or *in vivo*." While a *ts* phenotype often is associated with attenuation, it is not possible to predict that attenuation will indeed result, nor what its magnitude might be. This is considered by Dr. Murphy to represent "a critical deficiency" in the disclosure, since the level of attenuation *in vivo* is essential to assess the safety of a vaccine virus.

> Only by actually making an infectious recombinant virus, as provided in multiple working examples in the present disclosure, can one assess the *in vivo* attenuation of the virus to determine its usefulness as a vaccine candidate. Again, each of these deficiencies of Belshe et al. would have been clear to the skilled artisan and would have undermined the motivation and expectation of success for practicing the claimed invention following the teachings of Belshe et al.

Dr. Murphy further states in paragraph 14 of his Declaration that:

> Only with the aid of the present disclosure providing a successful cDNA recovery system can the phenotypic effect of any desired mutation (e.g., an attenuating mutation from PIV3 cp45) be evaluated and demonstrated. For example the instant disclosure demonstrates that a ts mutation identified in L can be segregated from complementary or interactive effects of other cp45 mutations. In this context, it is critical for evaluating the speculative teachings of Belshe et al. that at least a representative set of mutations identified and segregated into a viable recombinant vaccine candidate be verified as attenuating, and that such attenuation be balanced sufficiently to yield a protective immune response in susceptible hosts. The simple studies of Belshe et al. were limited to complementation of replication for a cp45 virus

> using a wild type L plasmid. These studies were only conducted *in vitro* using tissue culture cells, and were not validated by parallel studies *in vivo*. In this context, it was quite possible that recombinant viruses incorporating one or more of the three "temperature sensitive" (ts) mutations in the cp45 L gene mutations would not be attenuating (att) *in vivo*. In particular, a finding that replication of cp45 may be complemented by wild type L protein in tissue culture cells is not clearly predictive that a virus bearing one or more of these mutations would be attenuated *in vivo*.

This correlative deficiency noted by Dr. Murphy is stated by him in paragraph 14 of his Declaration to be apparent from the following considerations. First, it is known that entire classes of viruses called "temperature-dependent hose range (td-hr) mutants" may be ts on one tissue but not on other tissue culture cells. These td-hr mutants are not necessarily attenuated *in vivo* (see Snyder et al., Virus Research 15:69-84, 1990 and Shimizu et al., Virology 124:35-44, 1983). As described in Snyder et al., an exemplary mutant (clone 143-1) of influenza virus was shown to be highly ts in tissue culture cells, but was not significantly attenuated *in vivo*. Additional findings by Shimizu et al. indicate that such td-hr mutants are common and are found in many different complementation groups of the influenza virus (i.e., they are present in many different genes of the virus). Based on this and other evidence, Dr. Murphy renders the following conclusions:

> The Belshe et al. reference does not demonstrate whether any of the contemplated ts mutations in the L gene of cp45 belong in the td-hr class of mutations or in the other class of ts mutations whose replication is effected by the temperature present in the host animal. In view of this deficiency, the simple description of a complementation phenotype for a group of multiple, unsegregated mutations in a complete gene *in vitro* does not serve as a reliable indicator of attenuation *in vivo*. As detailed herein, the instant disclosure provides the basic tools, along with fully detailed description and guidance, to resolve these deficiencies and enable the skilled artisan to practice the invention throughout the scope of the claims presented for review.

Additional discussion is provided in paragraphs 15 and 16 of Dr. Murphy's Declaration pertaining to the requirement for fidelity in determining and

describing sequence information for cDNAs and plasmids to allow initial generation of a recombinant virus and validation of a successful recovery system. It is noted that the sequence of the cp45 L gene claimed by Belshe was taken directly from published work by others and were previously considered possible attenuating mutations. Those sequences were subsequently found to contain errors that were corrected by the present disclosure. The complete, correct sequence of cp45 is presented in current specification. This information, combined with the first successful attempt to generate recombinant PIVs containing various combinations of these mutations, defined the major attenuating mutations in PIV3 cp45 to be in the genes encoding not only the L protein, but also the C and F proteins. The present work also provided the first analyses of virus replication, immunogenicity and protective efficacy for these single and combinatorial mutants in accepted models for PIV infection and vaccine development. Examination of Figure 1 of the Belshe et al. patent fails to identify the mutation in C. The Figure only reiterates the incomplete sequence information and analysis previously reported by Stokes et al. From Belshe et al., one would not know that the F or C mutations present in cp45 were attenuating mutations, and that these mutations are useful in cDNA-derived recombinant vaccine viruses. The materials and methods described in the instant disclosure not only identified the attenuating mutations present in cp45, but provided a general method that later proved useful in identifying other attenuating mutations present in heterologous viruses such as a mutation designated 456 from the respiratory syncytial virus (RSV) L protein, a mutation designated 170 from the Sendai virus C protein, and a mutation designated 1711 mutation from the L protein of bovine PIV3 (BPIV3), for incorporation into recombinant PIVs of the invention. As summarized by Dr. Murphy at paragraph 15 of the Declaration:

> In this context, the Belshe et al. disclosure provided little new information on the nature of the genetic determinants of the ts phenotype of cp45--only following previous suggestions that one or more mutations in L might specify some portion of the ts phenotype in cp45. In contrast, by describing successful recovery of recombinant PIV from cDNA, and by further incorporating individual and combinatorial mutations from cp45 (from several genes as well as from extragenic portions of the genome) in recombinant PIVs, the instant disclosure dissects and maps

> out the specific contributions of the individual lesions in cp45 to the attenuation phenotype. Following introduction of these various, representative mutations, singly and in combination, into recombinant PIVs, the ability to achieve an attenuation phenotype using various manipulations, and to fine tune the attenuation phenotype to achieve useful vaccine strains, was established using widely accepted *in vivo* models for attenuation and immunogenic activity in humans.

As noted above, recovery of a recombinant virus from cDNA was not accomplished by Belshe et al. Nonetheless, the reference speculates even further concerning the prospect of chimeric "hybrid" recombinant vaccine viruses (see, e.g., Example 7). However, Belshe et al. clearly fail to describe or enable any chimeric cDNA constructs or methods for recovering chimeric viruses from cDNA, nor to characterize any chimeric viruses *in vitro* or *in vivo* for identification of useful vaccine candidates. As summarized by Dr. Murphy in paragraph 17 of his Declaration:

> Thus, although the principal disclosure of Belshe et al. purports to render construction of chimeric PIV and other "hybrid" viruses possible, the reference neither describes, teaches nor suggests the presently claimed subject matter. On the contrary, no specific guidance is provided to enable any kind of cDNA recovery of PIV, much less recovery of a viable, attenuated and infectious chimeric PIV as provided by the instant disclosure. The speculative teachings of Belshe et al. would not have been accepted by the skilled artisan as providing a clear teaching or practical motivation to achieve the presently claimed invention. This conclusion is underscored by the vast diversity of viral "targets" contemplated by Belshe et al. for constructing "hybrid" viruses . . ..
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> In contrast to these broad, prophetic and overreaching statements, the present specification provides detailed description and guidance, as well as a fully representative assemblage of working examples (e.g., various attenuated PIV3-1 chimeric vaccine candidates) that is fully commensurate with the scope of claims presented for review.

Additional differences between the present disclosure and the Belshe et al. reference relating to the description of a system to recover infectious replicating viruses from cDNA for selection as vaccine candidates are outlined in Tables 1–3 of Dr. Murphy's Declaration, and are briefly addressed in the subsequent paragraphs. Referring to Table 1 and paragraph 18 of the Declaration, it is noted that Belshe et al. fail to provide an accurate sequence of a wild type PIV virus. This is considered by Dr. Murphy to represent "a critical deficiency for describing and enabling the instantly claimed invention." Relating to this conclusion, PIV lacks a proof-reading polymerase and is known to have a high error rate. During cDNA cloning this high error rate is reflected in a relatively large number of sequence differences among clones, which are heightened by additional errors introduced during RT, PCR, and propagation in bacteria. A single point mutation in the 15.4 kb sequence can be sufficient to preclude recovery, and the identification and correction of potential errors presents "a formidable challenge." The sequences described in the prior art and incorporated by Belshe et al. were later modified by the instant disclosure to correct errors, and the ultimate recovery of infectious virus verified that the presently described sequence is "viable". Commenting on these facts, Dr. Murphy concludes as follows:

> Thus, Belshe et al. rely on the previously reported sequence by Stokes et al, and there was no evidence at the time that this sequence, shown in the present disclosure to be inaccurate, could have yielded a viable virus. Even if this untested, incorrect sequence were employed successful to obtain a recombinant virus, it was nonetheless unpredictable whether the sequence would specify a replication competent phenotype, i.e., a level of replication compatible with immunogenicity *in vivo*. Thus, Belshe et al. would not have been considered by the skilled artisan to enable recovery of a recombinant PIV3 nor a chimeric vaccine virus, since there was insufficient evidence that the reported sequence would yield these required results. Only the instant disclosure provides an authentic sequence of the full length PIV3 and its contiguous sequences in a plasmid with correct T7 promoter elements, T7 terminators, and hepatitis delta ribozyme. It is noteworthy that during the nearly seven years after the filing date of Belshe et al., Belshe and coworkers have apparently failed to recover any PIV from cDNA. In contrast, the instant disclosure provides a large, fully representative panel of recombinant

> viruses, including singly and multiply attenuated viruses and chimeric viruses. Among these recombinant viruses, PIV3 and PIV1 viruses and chimeric "vectors" have been constructed and demonstrated to be suitably attenuated and immunogenic to yield protection against PIV1, PIV2, and PIV3. Following these detailed teachings, our lab has progressed into clinical studies for PIV vaccine candidates recovered from cDNAs.

In further reference to Table 1, and to paragraph 20, of the Murphy Declaration, Belshe et al. also fail to describe or enable any specific sequence for an "insert" to yield a chimeric virus that would be compatible for efficient replication in a PIV3 backbone. Instead, Belshe et al. simply reference viral proteins, but do not specify any specific sequence of an insert, nor an insert length (see Belshe et al., columns 17–18). Dr. Murphy concludes that "[s]ince there were many sequence errors existing in the literature, it would not have been possible to determine whether the chimeric viruses phrophetically reported by Belshe et al. would be viable, or, if viable, would possess a replication competent phenotype, i.e., a level of replication compatible with immunogenicity *in vivo*." In contrast, the PIV1 sequences used in the construction of chimeric cDNAs of the present invention to generate a PIV3-1 virus were obtained from a wild type PIV1 of known virulence for humans and, following insertion into the PIV3 backbone, yielded a chimeric virus with a verified wild type phenotype. Dr. Murphy summarizes the attendant deficiencies of Belshe et al. as follows:

> The genes that encode the proteins alluded to by Belshe et al. include gene start sequences, a 5' non-coding region, coding region, 3' non-coding region, and gene-end sequence. The exact junctions of the sequences for the inserts referred to by Belshe et al. were not described and therefore one would not have known from the Belshe et al. description whether to include any of the extra-coding sequences or not. For example, the genes from any given virus contain transcription signals that differ from those of another virus, yet it is essential that the "transferred" gene be faithfully expressed in the new, heterologous viral backbone. This critical issue is not even addressed in the Belshe et al. specification. In contrast, the instant disclosure provides exemplary descriptions of an insert, backbone, transcription signals and junctions to yield viable chimeric PIVs that are useful vaccine candidates.

Yet another critical deficiency of Belshe et al. that is considered by Dr. Murphy to be resolved by the present disclosure relates to the length of the viral genome for production of recombinant PIVs (Murphy Declaration at ¶ 21). The length of the PIV genomes need to be an even multiple of six in order to recover authentic copies of virus containing the exact sequence in the cDNA. This "rule of six" reflects the association of each NP monomer with six nucleotides. If the genome does not conform to the rule of six, mutant viruses are recovered that have random mutations that correct the length. According to Dr. Murphy:

> [T]his factor adds a major aspect of uncertainty to the teachings of the Belshe et al. reference, which fails to appreciate the significance of the rule of six and the errors that would arise by failure to properly construct cDNAs in accordance with this requirement." In the instant disclosure, the exact lengths of a full length cDNA for PIV3 (number of nucleotides = 15462) and for PIV3-1 (number of nucleotides = 15516) are provided. This description in turn depended on the actual, successful recovery of recombinant PIVs and subsequent analysis and verification of the fidelity of the viral sequence and phenotype.

As further emphasized by Dr. Murphy, the specific methods used to recover infectious virus also need to be described to enable production of recombinant viruses from cDNAs. Systems to recover negative stranded RNA viruses such as PIV from cDNA are complicated and require a suitable cell capable of both successful transfection by plasmids and replication of the rescued virus. Dr. Murphy notes that "the recovery of infectious recombinant negative stranded RNA viruses is generally quite inefficient", such that out of 1,000,000 transfected cells, 10 or fewer cells actually produce virus. Particularly for a human pathogen such as PIV3, which does not grow rapidly *in vitro*, it is "a formidable challenge" to successfully produce and recover recombinant virus from cDNA. Considering these factors, Dr. Murphy states that:

> Our studies confirmed that the precise amount of the viral cDNA and support plasmid DNA was critical for initial recovery of recombinant PIV, and this factor was not appreciated by Belshe et al., who failed to even initiate a recovery system. As another example of inadequate guidance, Belshe et al. describe prophetically the use of cDNA expressing a genome sense RNA to recover virus

> (column 10, line 35). It is now known, however, that for technical reasons the recovery of virus from genome-sense RNA is relatively inefficient at best, and often unsuccessful. An optimal strategy employs a cDNA expressing a positive sense copy of the genome (called an antigenome). This guidance is clearly provided in present disclosure.

In paragraph 23 of his Declaration, Dr. Murphy focuses on the requirement for a complete description of a system to promote expression of viral proteins from support plasmids and from a full-length cDNA to form a functional transcriptase/replicase/genome complex, without which disclosure production of a recombinant PIV from cDNA would not be enabled. Such a "full description" of this system is considered by Dr. Murphy to be lacking in the disclosure of Belshe et al. For example, the system described by Belshe et al. uses a replication competent vaccinia virus expressing T7 (Column 15 of Belshe), but it does not specify how a viable PIV virus would be recoverable in the presence of a vast excess of fully infectious, replication-competent vaccinia virus. Dr. Murphy concludes that "[I]t is unlikely that a low concentration of a recombinant PIV could be biologically separated from the replication-competent vaccinia." This is especially true since vaccinia virus is highly permissive for most cell types and is extremely difficult to fully neutralize with antibody. In contrast, in the methods described in the instant disclosure recognize and employ a replication deficient vaccinia virus (MVA-T7). This adaptation permitted the successful recovery of a recombinant PIV in the presence of the MVA-T7.

> Thus, Belshe et al. did not describe a system that would have been considered capable of successfully recovering recombinant PIV from cDNA, particularly attenuated (or attenuated, chimeric) viruses having further restrictions on replication. (Murphy Declaration at ¶ 23).

Additional discussion provided in Dr. Murphy's Declaration (at ¶ 24) points to the significant "complexities and uncertainties" that were overcome by Dr. Murphy and his coinventors to achieve successful recovery of PIV from cDNA. In particular, Dr. Murphy cites to extensive and often unsuccessful work by others in the field attempting to achieve recovery of other infectious recombinant negative strand RNA viruses. For example, despite extensive foundational research and discovery aimed at

recovering a recombinant measles virus, successful production of the recombinant virus from cDNA was not reported until 5- to 6-year after Ballart et al. (EMBO J. 9:379, 1990) reported construction of a complete cDNA expressing the genome of measles virus under the control of a T7 promoter and the recovery of recombinant virus by complementation of this synthetic genome with intracellularly-expressed measles virus proteins. Notably, this report, which parallels in certain aspects the prophetic disclosure of Belshe et al., proved to be in error and was retracted. The long delay in achieving a successful measles virus recovery system after the general strategy for recovery was mapped out by Ballart and coworkers underscores "the formidable technical and conceptual challenges that must be met to achieve a successful recovery system" for any negative stranded RNA virus (Murphy Declaration at ¶ 24). In fact, at this stage of development in the art, "there was genuine concern that successful recovery of any negative strand virus might not be feasible." Thus, the successful recovery of recombinant rabies rhabdovirus in 1994 (Schnell et al 1994 EMBO J. 13:4195) was a "major milestone" (Id.) However, it was not clear whether this would be successful with paramyxoviruses, which have substantially greater genome size and complexity, more complex sets of protein products, and poorer growth and stability. In work with a second virus, the highly efficient rhabdovirus vesicular stomatitis virus (VSV), it was shown in 1990 that plasmid-expressed proteins could support a biologically derived nucleocapsid (Pattnaik et al, 1990 J. Virol. 64:2948), but two more years were required to develop the capability to express a defective interfering particle from cDNA (Pattnaik et al, 1992 Cell 69:1011) (Id.) Three more years were required to express complete infectious recombinant virus (Lawson et al 1995 Proc. Natl. Acad. Sci. USA 92:4477; Whelan et al, 1995 Proc. Natl. Acad. Sci. USA 92:8388), which also was viewed as "a major achievement" (Roberts and Rose 1998 Virology 247:1). The work with the rhabdoviruses rabies and VSV involved unexpected requirements, such as the need to express the genome in positive sense form, the need to avoid structures causing early termination by the T7 RNA polymerase, and the need to reduce the background of vaccinia virus. Summarizing these developments, Dr. Murphy states as follows:

> In many instances, recovery depended on methods that could not be applied generally to other viruses, such as removal of the vaccinia virus background by filtration

(Schnell et al 1994 EMBO J 13:4195, Lawson et al, ibid), which could not be applied to paramyxoviruses because of their large size and hence necessitated the development of alternative strategies. Studies in other nonsegmented negative stranded viruses illustrate still other unexpected requirements, such as the need to express an additional protein, the M2-1 protein, to achieve successful recovery of human respiratory syncytial virus (Collins et al, 1999, Virology 259:251). This brief survey of the literature embraces only to a subset of studies I know to have been undertaken in large numbers of labs across the globe seeking to recover negative stranded RNA viruses from cDNA. Many of those labs that never came close to successful recovery, thus their efforts have gone unreported. In summary, myriad challenges have persisted in the art to development of a successful recovery system for PIV. These chalienges underscore the deficiencies of Belshe et al., who provide only vague, generic concepts without documentary experimentation nor demonstration of a feasible recovery system for PIV. At the same time, the slow-developing state of the art, and the high level of unpredictability in the field, emphasize the unexpected nature of results provided within the instant disclosure.

In the closing paragraphs (¶¶ 25-26) of his Declaration, Dr. Murphy briefly contrasts the instant disclosure with that of Belshe et al. in the context of characterizing the in vivo activity of a recombinant PIV recovered from cDNA. In this context, Dr. Murphy emphasizes that "[t]he properties of the virus that make it a successful vaccine candidate must be described in detail in a representative assemblage of recombinant species, as provided by the instant disclosure." He points to three possible consequences that can occur when one attempts to recover a wild type PIV3 or a chimeric recombinant virus from cDNA: (1) a recombinant virus is recovered that replicates to levels characteristic of wild type virus or indicative of attenuation; (2) a recombinant virus is recovered that contains one or more inadvertent and unknown sequence errors that render it defective in any of a number of ways; and (3) virus is not recovered, due either to one or more lethal sequence errors or some deficiency in the recovery strategy or conditions. In addition, when one introduces mutations into such a cDNA intended to attenuate the virus and thereby to render it useful as a vaccine candidate, at least four outcomes are possible: (1) one can increase the virulence of the virus; (2) one can

incompletely attenuate the virus; (3) one can achieve a satisfactory level of attenuation such that a virus can be used as a vaccine; and (4) one can over-attenuate a virus or render it non-viable. In reference to the current specification, Dr. Murphy states that:

> The examples provided in the instant specification fulfill criterion 3 by providing a representative assemblage of recombinant viruses that are suitably attenuated for development as vaccine agents. In contrast, the disclosure of Belshe et al. fails to achieve any of the foregoing possibilities--by virtue of its failure to describe and enable a cDNA construct encoding a recombinant PIV (see Table 1), for failing to recover infectious virus from cDNA (Table 2), and for the lack of testing and characterization of an infectious, recombinant virus (Table 3).

By way of contrast, the Belshe et al. specification provides only a limited description concerning the use of a plasmid expressing a wild type PIV3 L protein to enhance replication of a JScp45 virus at a restrictive temperature of 39.5°C. According to Dr. Murphy:

> This limited disclosure does not provide a reasonable scientific basis for the speculation by Belshe et al. that the L gene of cp45 possesses mutations that might be useful in a recombinant PIV vaccine virus derived from cDNA. The virus recovered by Belshe et al. after complementation with the L-encoding plasmid at the restrictive temperature was not changed or modified in any manner as contemplated by Applicants' disclosure. No cDNA constructs were designed and produced from which PIV3 wild type viruses could be recovered, and certainly no new constructs or recombinant viruses bearing a chimeric genome or antigenome, and/or specific, attenuating mutations were described or enabled. The absence of such disclosure in the Belshe et al. reference negates any "reasonable expectation for success" to achieve the presently claimed invention in either its independent or dependent aspects. This is especially clear when the particular results provided by the instant disclosure are appreciated, namely that it was shown to be possible to construct a panel of recombinant PIVs, including singly and multiply attenuated and chimeric viruses, from cDNA that are suitably attenuated and immunogenic for development as vaccine candidates.

In view of the foregoing evidence and remarks, Applicants respectfully submit that the disclosure of Belshe et al. does not teach or suggest production in a

cDNA-based recovery system of an infectious PIV, particularly a recombinant PIV that is suitably attenuated by incorporation of one or more recombinantly introduced mutation(s), or by other methods disclosed in Applicants' specification. Nor does the Belshe et al. reference teach or suggest yet more challenging aspects of Applicants' invention, such as production of infectious, multiply attenuated and attenuated, chimeric PIVs for use in vaccine formulations. The simple complementation assays described by Belshe et al. using the biologically derived mutant cp45 virus and a wild type L plasmid, was only conducted *in vitro* using tissue culture cells, and was not validated by parallel studies *in vivo*. From this disclosure, the report that replication of cp45 can be complemented by wild type L protein in tissue culture cells does not amount to a reasonable scientific forecast that a recombinant virus bearing one or more of the cp45 mutations would be attenuated *in vivo*.

This correlative failure and other deficiencies of the Belshe et al. reference noted in the record clearly evince that the alleged teachings of Belshe et al. are inoperable for production of a recombinant PIV from cDNA. Moreover, the reference fails to provide a sufficient suggestion in the form of "practical motivation", as required, to render the invention obvious within the meaning of 35 U.S.C. ¶ 103. This determination correlates with evidence presented in the record that the skilled artisan would not have had a "reasonable expectation of success" to follow the teachings of Belshe et al., with the application of available knowledge in the art, to achieve the instantly claimed invention. Also supportive of this determination is the Office's own findings concerning predictability and enablement of the subject technology, which obstacles were only been resolved commensurate with the scope of the pending claims by Applicants' extensive and surprising disclosure (see enablement discussion, below).

Finally, even if one considers that the Belshe et al. reference may have provided a suggestion to attempt recovery of recombinant PIV from cDNA, the facts of record establish that such suggestion amounted, at best, to an "invitation to experiment", whereas the results set forth in Applicants' disclosure clearly represent "unexpected results" sufficient to overcome any prima facie case of obviousness based on the art of record. In view of these and other controlling facts and authority presented in the record,

Applicants respectfully submit that the rejection of claims 1-4, 6, 7, 10-17, 20, 21, 26, 27, 30, 33-40, 43, 44, 47-49, 52, 54, 56, 57, 59, 6185, 88-91, 93, 94, 96-116, 118, 120-143 under 35 U.S.C. 102(e) as allegedly anticipated by or, in the alternative, under 35 U.S. C. 103 (a) as allegedly obvious over, Belshe et al (5,869,036), has been overcome.

Claims 51 and 53 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Belshe et al, for reasons of record. Applicants respectfully submit that the basic cDNA recovery method, yielding an infectious PIV particle, as set forth in claim 48 is patentable over Belshe et al. for the reasons noted above. Claims 51 and 53 depend directly or indirectly from claim 48 and necessarily include all elements and limitations therein. Therefore, claims 51 and 53 are also patentable over Belshe et al., irrespective of the merits of the Office's discussion regarding single versus multiple vector expression systems, which need not be addressed here.

Claims 18, 19, 28 and 29 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Belshe at al., or, in the alternative, under 35 U.S.C. § 103(a) as allegedly obvious over Belshe et al. in view of Stokes et al. (Virus Research 30:43-52, 1993). Applicants respectfully traverse. In this regard it is submitted that the teachings of Belshe et al. do not render the subject matter of the rejected claims anticipated or obvious, for the reasons noted above. Further, there is no additional disclosure in the Belshe et al. or Stokes et al. references that would render recombinant PIV having specific substitutions in the N protein enabled or provide a reasonable expectation of success for achieving such recombinants having the characteristics disclosed by Applicants.

Claims 22-25, 31, 32, 42, 60, 117, and 119 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Belshe et al. in view of Conzelman (J. Gen. Virol. 77:381-389, 1996). The teachings of Belshe et al. do not render the subject matter of the rejected claims anticipated or obvious, for the reasons noted above. The general review publication by Conzelman does not add to the disclosure of Belshe et al. to an extent that would enable the subject claims or provide a reasonable expectation of success for achieving the claimed subject matter and results disclosed by Applicants.

Applicants acknowledge that the Office has reconsidered and withdrawn the rejection of claims 11, 48, 50, 52, 55, 56, 58, under 35 U.S.C. 102(b) as allegedly anticipated by Dimock et al (Journal of Virology 67:2772-2778, 1993), is withdrawn in view of applicant's arguments and amendments to the claims.

Claims 91 and 92 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Dimock et al. (J. Virol. 67:2772-2778, 1993), for reasons of record. The subject claims have been amended to clarify that the PIV particles of the invention are "self-replicating" as distinguished from the defective particles obtained via the minigenome system of Dimock et al. As noted previously in the record, the Dimock et al. reference discloses a limited, minigenome system for recovering synthetic "analogs" of genomic RNA and replicative-intermediate RNA of HPIV3. The reference clearly does not disclose the infectious, self-replicative particle of amended claim 91. Accordingly, withdrawal of the rejection is earnestly solicited.

Double Patenting

Claims 1-94 and 96-143 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-6, 8-45, 47-50 of copending Application No. 09/458,813, and copending Application No. 09/459,062, for reasons of record. Claims 1, 2, 5-10, 33-42, 73, 74, 76-80, 83, 88, 89, 97-99, 107-111, 122, 123, and 141 are also provisionally rejected for obviousness-type double patenting. Applicants note the provisional nature of these rejections and will take appropriate steps to address the Office's concerns upon indication of allowable subject matter in one of the subject applications.

Claims 1-94 and 96-143 are considered by the Office to conflict with claims 1-94 and 96-128 of Application No. 09/424,628. Applicants will review the subject claims of the two applications to ensure that conflicting subject matter is not maintained in both cases.

New Grounds of Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-94 and 96-143 are rejected under 35 U.S.C. 112, first paragraph. The Office contends that the specification, while being enabling for the viruses disclosed in the working examples, does not reasonably provide enablement for the full scope of viruses encompassed by the claims. The Office cites an out-of-context statement by Applicants' representative that "useful mutations for incorporation in Applicant's recombinant vaccines can only be defined by actual recovery of the mutations in a recombinant virus, and by demonstration that the mutations specify desired phenotypes in the recombinant virus"--as a basis to support a blanket determination of nonenablement for all species within the scope of the claims that have not been specifically exemplified by working examples in the disclosure.

As a preliminary point in rebuttal, it seems paradoxical that the Office continues to assert the Belshe et al. reference as allegedly anticipatory, while rejecting Applicants' disclosure (containing 128 pages of detailed description including 82 pages of working examples) as allegedly nonenabling. The Office concedes that the Belshe et al. reference lacks any working examples of a recombinant PIV, much less of a single or multiply attenuated, or chimeric PIV. To anticipate the instantly claimed invention, Belshe et al. must fully describe and enable the subject matter of the pending claims. Applicants therefore request clarification as to what the Office considers to constitute an enabling disclosure of the subject technology, particularly in view of the correct standard of proof for which clarification is also requested above.

Turning to the issue of enablement as it relates to Applicants' disclosure, the accompanying Declaration of Dr. Brian Murphy clarifies that the specification provides full, enabling support commensurate with the scope of claims presented for review. It is not true that Applicants have set "their own precondition for enablement" as stated by the Office, where only those recombinant PIV species "defined by actual recovery in a recombinant virus" can be considered enabled by the disclosure. This amounts to a legal conclusion that is not within Applicants' purview to render, and it further ignores the facts of the case as well as controlling legal authority concerning

applicable standards for enablement review. In this regard, Applicants firmly traverse for the record the Examiner's statement at page 12 of the Office Action, as follows:

> Applicant's opinion of the state of the art and the unpredictability of the art does not constitute clear and convincing evidence that one skilled in the art would not have been able to produce the materials of the patent claims using the disclosure of the patent specification and routine experimentation. Absent clear and convincing evidence to the contrary, the patent claims are presumed enabled, and in the face of this presumption applicant's claims remain rejected as anticipated by the patent claims, or as obvious over the patent claims as stated above. Further, each application is considered on its own merits, and the merits for this application include applicant's own characterization of the state of the art and the predictability of the art, which are factors to be considered in regard to enablement of the claims in this application.

Applicants' prior response, to which the Office refers, was rendered in the context of characterizing the limited disclosure of Belshe et al., and was not intended as a blanket standard for enablement to be applied against the pending claims in a vacuum. It is clear that Applicants' disclosure presents an entirely different stage for analysis of enablement with respect to singly and multiply attenuated and chimeric recombinant PIV vaccine constructs--by virtue of providing detailed description and extensive working examples demonstrating a representative assemblage of proven, characterized recombinant PIVs that is fully commensurate with the scope of claims presented for review. The notion that the so-called "merits" of the Belshe et al. patent are to be weighed differently (e.g., so as to be exempted from a requirement for working examples--see Office Action Paper No. 17, pp. 5-7, while Applicants are held to a requirement to describe and characterize every species within the scope of the claims) is clearly improper. Rather, the same factual inquiries concerning the state of the art, predictability of the subject matter, presence of working examples, etc. (see Applicants submission of April 5, 2001, pp. 13-16), should be applied equally in evaluating these respective disclosures. Belshe et al. is therefore not exempt from any "admissions" that may have been made by Applicants—such statements, only when properly construed, must be accepted or rejected as factual points in the record, to be applied to both subject cases under consideration in view of the different teachings of the respective disclosures.

Presently, the framework for this analysis seems to be reversed, where so-called admissions are applied adversely only to Applicants disclosure that far surpasses the Belshe et al. reference in its level of direction and guidance. In this regard, the Office is again urged to reconsider and clarify the burden of proof presently imposed upon Applicants requiring "clear and convincing evidence" that Belshe et al. is inoperative to achieve the presently claimed subject matter (see above).

General Standards for Enablement Review

To properly evaluate Applicants' disclosure, the enablement requirement of 35 U.S.C. § 112 only requires that there be a "reasonable correlation" between the disclosure and the scope of protection sought in the claims, having due regard for the nature of the invention and the state of the art. (See, e.g., In re Vaeck, 20 USPQ2d 1438 (Fed. Cir. 1991); Ex parte Jackson, 217 USPQ 804, 807 (Bd.Pat.App.Int. 1982); In re Fisher, 166 USPQ 18, 24 (CCPA 1970); MPEP § 706.03(n)). A disclosure is entitled to a presumption that it satisfies the enablement requirement, which presumption is only overcome by scientific evidence that is "inconsistent with" Applicants' teachings. In re Marzocchi et al., 169 USPQ 367 (CCPA 1971). As further explained in the PTO's Enablement Guidelines, (see, e.g. Example 5E: "Peptides for Treating Obesity"):

> The Office must accept as being true the statements supporting enablement unless there is an objective reason, usually supported with documentary evidence, to question them.

Where there are multiple modes disclosed for practicing an invention, the challenger:

> can carry its burden only by showing that all of the disclosed alternative modes are insufficient to enable the claims, because `[t]he enablement requirement is met if the description enables any mode of making and using the claimed invention.'

Johns Hopkins University v. Cellpro Inc., 47 USPQ2d 1705, 1709 (Fed. Cir. 1998) (quoting Engel Industries Inc., v. The Lockformer Co., 20 USPQ2d 1300, 1304 (Fed. Cir. 1991).

For the purpose of enablement, a patent specification is not required to function as a "blueprint which, if followed, would unfailingly reproduce exactly an

applicant's claimed invention." Staehelin v. Secher, 24 USPQ2d 1513, 1516 (Bd.Pat.App.Int., 1992). As stated in In re Gay, 135 USPQ 311, 316 (CCPA 1962):

> . . . Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be.

See also, Phillips Petroleum v. U.S. Steel, 6 USPQ2d 10065, 1073 (D. Del. 1987) ("[B]ecause an application speaks to those skilled in the art, it need not set forth every minute detail regarding the invention).

Other cases clearly emphasize that a requirement for comprehensive disclosure of all possible species and modes of practicing an applicant's invention is contrary to the central policy of U.S. patent law, i.e., to promote the useful arts. This policy is specifically permissive in the case of biomedical inventions. As noted by the Board in Ex parte Aggarwal, 23 USPQ2d 1334 (Bd. Pat. Appl. Inter. 1992) that:

> Case law subsequent to Brenner is receptive to early filing of applications in the biomedical field . . ..(Referencing Brenner v. Manson, 383 U.S. 519 (1966)).

In accordance with this policy principle, the PTO's Enablement Guidelines state at Section III(A)(2), as follows:

> As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of Section 112 is satisfied. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under Section 112. Spectra-Physics, Inc. v. Coherent, Inc. 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.) *cert. denied*, 484 U.S. 954 (1987).

A similar standard was articulated by the Federal Circuit in U.S. v. Teletronics Inc., 8 USPQ2d 1217, 1223 (1988):

> Since one embodiment is admittedly disclosed in the specification, along with the general manner in which its current range was ascertained, we are convinced that other permutations of the invention could be practiced by those skilled in the art without undue experimentation.

See also, Johns Hopkins University v. Cellpro Inc., 47 USPQ2d 1705,1719 (Fed. Cir. 1998) (quoting Engel Industries Inc., v. The Lockformer Co., 20 USPQ2d 1300, 1304 (Fed. Cir. 1991) ("The enablement requirement is met if the description enables any mode of making and using the claimed invention.")

A comprehensive species disclosure requirement for generic inventions was also criticized by the Federal Circuit's predecessor court in In re Angstadt and Griffin, 190 USPQ 214, 218 (CCPA 1976):

> [S]uch a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims . . ..

In this context, the Angstadt panel held that a patent applicant is "*not* required to disclose *every* species encompassed by their claims even in an unpredictable art." (Id.) (emphasis in original).

As further explained in the Enablement Guidelines, at Section III(B)(2):

> The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. (citing Atlas Powder Co. v. E.I. duPont de Nemous & Co., 750 F2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)).

Likewise, the district court in Phillips Petroleum Co. v. U.S. Steel Corp., 6 USPQ2d 1065, 1074 (D. Del. 1987) held that:

> A patent applicant is not required, however, to predict every possible variation, improvement or commercial embodiment of his invention. (citing SRI Intern. v. Matsushita Elec. Corp. of America, 227 USPQ 577, 586 (Fed. Cir. 1985), and Hughes Aircraft Co. v. United States, 291 USPQ 473, 481 (Fed. Cir. 1983).

See also, Douglas v. United States, 184 USPQ 613, 615 (Ct. Cl. 1975).

> Nor can a patentee be expected to foresee every technological problem that may be encountered in adapting

> his idea to a particular use. Some experimentation and exercise of judgment is to be expected.

As further explained in Ex parte Naujoks, 17 USPQ2d 1537, 1540 (Bd. Pat. App. Int. 1989) (quoting with approval In re Michalek, 34 CCPA 1124 (1947)):

> [I]t is to be presumed that a process, if used by one skilled in the art, will produce the product alleged by the patentee and such presumption is not overcome by a mere showing that it is possible to operate within the disclosure without obtaining the alleged product. Skilled workers would as a matter of course, in our opinion, if they do not immediately obtain desired results, make certain experiments and adaptations . . .. [T]he failures of experimenters who have no interest in succeeding should not be accorded great weight. (emphasis added).

In this regard, enablement is not defeated by a requirement for some experimentation to practice an invention. In fact, "a considerable amount of experimentation is permissible," so long as the experimentation is not "undue." Ex parte Jackson, 217 USPQ 804, 807 (Bd. Pat. App. Int. 1982).

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. . . .. Id., citations omitted).

Thus, reasonable experimentation to practice a working embodiment of an invention can be as complex, difficult and time consuming as is ordinarily considered "reasonable" in the art, and that does not require "ingenuity beyond that to be expected of one of ordinary skill." (See, e.g. Atlas Powder Co. v. E.I. duPont de Nemous & Co., 224 USPQ 409, 414 (Fed. Cir. 1984). As emphasized in the above-cited above in the case of In re Michalek, 34 CCPA 1124 (1947):

> Skilled workers would as a matter of course, in our opinion, if they do not immediately obtain desired results, make certain experiments and adaptations . . ..

Considering the present case, Applicants submit that their disclosure provides extensive direction and guidance and a full complement of tools to implement and adapt the teachings of the specification to produce a large variety of operable PIV vaccine candidates commensurate with the scope of the claims. The Office has proffered no evidence beyond an out of context statement by Applicants' representative to show that it would be unreasonable, or that it would require ingenuity beyond that of the ordinary artisan, to obtain a representative assemblage of operable species commensurate with the instant claims. On the contrary, Applicants maintain that such a representative assemblage of species is already provided within the working examples of the specification, and the record is clear that additional species within the invention can be produced and evaluated without undue experimentation. These conclusions are clearly supported by the accompanying Declaration of Brian R. Murphy, which reads in pertinent part (see, ¶ 27 and preceding discussion) as follows:

> Concerning the issue of enablement, the foregoing discussion clearly establishes that the application provides extensive description, guidance, and working examples that teach the skilled artisan how to make and use recombinant PIVs from cDNA in a manner that is reasonably correlated with the full breadth of the claims. Numerous recombinant PIVs are described and tested in accepted model systems. For example, the instant disclosure details five attenuating mutations from the cp45 mutant that are identified, incorporated, and directly characterized in a recombinant PIV of the invention. Three of these mutations, identified in three different genes (C, F, and L), were shown to specify temperature sensitive attenuating mutations, while two others were demonstrated to specify non-ts attenuating mutations. Through the use of our novel PIV recovery system, the ability of these mutations to independently confer the property of attenuation on a recombinant virus in the absence of other cp45 mutations was proven. These studies fully evince the general usefulness of these mutations for attenuating recombinant vaccine viruses, including chimeric recombinant vaccine viruses, of the invention. At the same time, these studies clearly establish that a skilled artisan, following the teachings of the instant disclosure, will be enabled to identify additional useful mutations for incorporation within recombinant PIV vaccine viruses of the invention, without undue experimentation. In particular, the successful recovery of a

> representative assemblage of useful recombinant PIV vaccine candidates shown here provides strong motivation and clear, detailed guidance to render any such experimentation as needed to obtain additional species within the generic scope of the instant claims "reasonable" and attended by a high expectation of success. That certain species may be less optimal than others, or even inoperable, does not negate the broad utility and scope of the invention in this context. The poorly developed state of the art and high degree of unpredictability that existed prior to the current invention is no longer extant. On the contrary, these barriers have been lowered sufficiently that the skilled artisan, availed of the teachings of the instant specification, can practice the invention throughout its scope without such extensive and/or uncertain experimentation that would be considered "undue" or unreasonable.

On the basis of this evidence, and further in reference to the detailed description and working examples (pp. 47-128, incorporated herein by reference) provided in the specification, reconsideration of the rejection of claims 1-94 and 96-143 under 35 U.S.C. 112, first paragraph is respectfully requested. To clarify the record pertaining to enablement of recombinant PIVs of the invention, the Office is further urged to provide direct scientific evidence and reasoning for all of the relevant factors considered. In this context, Applicants' alleged "admission" relating to the level of predictability in the art does not qualify as evidence in the manner relied upon by the Office. In particular, this alleged admission was expressly limited to the predictability for achieving chimeric PIV vaccines prior to Applicants' invention. As stated by Applicants' representative, the lack of predictability pertained only to the art as viewed before Applicants' filing date, "without specific data such as the results disclosed in Applicants' specification teaching, e.g.. a viable PIVl-PIV3 chimera." It is therefore unfounded to interpret Applicants' remarks in this context as an admission that the level of predictability in the art facing Applicants in the present case remains similarly unpredictable as prior to their ground-breaking disclosure. On the contrary, the record should clearly reflect that Applicants' expectations for success were justifiably heightened by their extensive working examples proving successful construction of a representative panel of viable attenuated, multiply attenuated, chimeric, and attenuated

chimeric PIV constructs within the claims--including viable attenuated HPIV3-1 chimeras and even more challenging recombinant constructs incorporating various combinations of attenuating mutations from JS cp45.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-332-1380.

Respectfully submitted,

Dated: August 26, 2002

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APPENDIX, VERSION WITH MARKINGS
TO SHOW CHANGES MADE

91. (Twice Amended) An isolated infections self-replicating PIV particle which comprises a recombinant human or bovine PIV genome or antigenome, a N protein, a P protein, and a L protein.

111. (Amended) The isolated infectious PIV particle of claim 109, wherein said chimeric genome or antigenome incorporates at least one and up to a full complement of mutations present in rcp45, rcp45 3'NCMFHN, rcp45 3'NL, rcp45 3'N, or rcp45 F other than mutations in HN and F, selected from i) substitutions specifying a replacement of His for Tyr942, Phe for Leu992, and Ile for Thr1558 in the polymerase L protein; ii) substitutions specifying a replacement of Ala for Val96 and Ala for Ser389 in the N protein; iii) a substitution specifying a replacement of Thr for Ile96 in the C protein iv) mutations in a 3' leader sequence comprising a T to C change at a position corresponding to nucleotide 23 of JS cp45, a C to T change at nucleotide 24, a G to T change at nucleotide 28, and a T to A change at nucleotide 45 of JS cp45; and v) a mutation in an N gene start sequence comprising an A to T change at a position corresponding to nucleotide 62 of JS cp45.